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Cement mantle thickness does not influence serum or local gentamicin concentrations in hybrid total hip arthroplasty: a randomised controlled trial

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Abstract

Introduction: We investigated the *in vivo* gentamicin elution kinetics of Hi-Fatigue Gentamicin Bone Cement (AAP Biomaterials GmbH) in serum and drain fluid after hybrid hip arthroplasty and the relationship with cement mantle thickness.
Methods: We compared in a randomised, non-blinded prospective study, the local and systemic gentamicin concentrations in 2 groups. The thin cement mantle group (n = 16) received a stem implanted line-to-line with the broach, whereas the thick group (n = 14) had an undersized stem. Gentamicin concentrations were measured in drain fluid and serum at set intervals for 3 days postoperatively.
Results: In both groups, local gentamicin concentrations were similar. After a high initial burst above the minimal inhibitory concentration (thin: 57.2 mg/L (SD 34.4), thick: 54.9 mg/L (SD 19.9), p = 0.823) local gentamicin concentrations declined rapidly. In both groups, serum concentrations never exceeded toxic levels (maximum 1.08 mg/L).
Conclusion: In hybrid total hip arthroplasty, Hi-Fatigue Gentamicin Bone Cement resulted in effective and safe gentamicin concentrations.
Clinical trial protocol number: PMCI 12/02.

Keywords

Bone cement, gentamicin, hip arthroplasty

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Introduction

Cemented total hip arthroplasty (THA) leads to excellent long-term results, but deep infections remain a major concern.[1,2] Such infections account for 13.5% of all reoperations in the Swedish Hip Arthroplasty Register and are the second reason for reintervention.[3] Adding antibiotics to the cement can reduce the incidence of deep postoperative wound infections but there is a risk of allergic reactions, systemic toxicity, selection of resistant organisms and decreased mechanical strength of the cement.[4–6]

In general gentamicin is added to the cement because it is heat resistant and active against most common pathogens found in THA infections, i.e. *Staphylococci, Enterococc*i and *Pseudomonas.*[7,8] The minimal inhibitory concentration (MIC) of gentamicin is the lowest concentration that inhibits the visible bacterial growth after overnight incubation.[9] For *Staphylococci* the MIC ranges from 0.25 to 1 mg/L, for *Enterococci* it is 8 mg/L and for *Pseudomonas* 5 mg/L.[9–11] In

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Table 1. Composition of the Hi-Fatigue Gentamicin Bone Cement according to the manufacturer.

Components in the powder	Mass percentage
Poly(methylacrylat-methylmethacrylate)	27.54 %
Poly(methylmethacrylate-Styrene)	57.49 %
Zirconium dioxide	11.98 %
Benzoyl peroxide	0.83%
Gentamicin sulphate	2.16 %
Components in the liquid	**Mass percentage**
Methylmethacrylate (stabilised with 60 ppm hydroquinone)	99.35 %
Dimethyl-para-toluidine	0.65 %

order to be effective, the local gentamicin concentration around the implant should exceed the MIC. To be safe, the antibiotic elution from the cement should result in serum gentamicin concentrations beneath the toxic levels for prolonged exposure, i.e. 2 mg/L.[12,13]

Depending on the stem-broach sizing, cemented femoral hip implants can result in a thick or thin cement mantle.[14] Using a stem that is undersized compared to the last broach will create a thicker cement mantle, than when the implant is inserted line-to-line.[15] As thick cement mantles might contain more cement and antibiotics, they could theoretically lead to higher local but also higher systemic antibiotic concentrations. On the other hand, antibiotic elution from cement is known to be related to the contact area and surface roughness, the cement porosity, the antibiotic concentration and the composition of the cement.[16–20] If these factors would be the most important, the thickness of the cement mantle, i.e. the amount of cement/antibiotics, should have only a minor impact on the local and systemic antibiotic concentrations.

This randomised controlled trial (RCT) (clinical trial protocol number: PMCI 12/02) investigates the *in vivo* gentamicin elution from a low viscosity, high styrene containing, bone cement (Hi-Fatigue Gentamicin Bone Cement [HFGBC], [AAP Biomaterials GmbH]) that has not been investigated before. We compared the time dependent local and systemic gentamicin concentrations resulting from a thin and a thick cement mantle and explored factors that could influence these concentrations. The null hypothesis was that there is no difference in the *in vivo* elution of gentamicin from HFGBC irrespectively of cement mantle thickness.

Methods

Trial design and patient inclusion criteria

The study is a randomised, non-blinded, comparative and prospective clinical investigation. We included patients over 50 years of age, who gave informed consent and were scheduled for a hybrid total hip replacement, i.e. a cemented stem and an uncemented cup. Patients were excluded when they had been treated with gentamicin within the past 7 days, presented with a malignant fracture or had known allergies against constituents of the bone cement we used. Patients with renal impairment defined by an estimated glomerular filtration rate (eGFR) of less than 30 ml/minute, or patients who previously underwent a nephrectomy or renal transplant were excluded as well.

Interventions

After inclusion patients were assigned by computer to 1 of the 2 parallel treatment groups. Patients in the thick cement mantle group received a CPT femoral stem (Zimmer, Warsaw) that was undersized compared to the last corresponding broach.[14,21] Patients in the thin cement mantle group received a Vectra III femoral stem (Biomet, Warsaw) that was inserted line-to-line compared to the last corresponding broach.[14] Both femoral stems were fixed with Hi-Fatigue G Bone Cement (AAP Biomaterials GmbH). Cementing was performed with 3rd generation pressurisation technique but without the use of a sponge soaked in a diluted adrenaline solution and using the MIXIGUN Hybrid system (Zimmer).[22] All patients received an uncemented Trilogy cup (Zimmer) with a ceramic-on-ceramic bearing surface and were operated through a standard posterior approach by a senior orthopaedic surgeon (TS). Adverse events, if occurred, were documented and dealt with.

Cement

Hi-Fatigue Gentamicin Bone Cement has been registered since 2008 as a class III medical device. HFGBC consist of 2 separate sterile components (Table 1). When mixed together, they become a fast hardening, radiopaque, high fatigue bone cement.

To estimate the amount of cement used to fix the femoral stem we averaged the weight of 3 measurements of the total amount of cement together with the MIXIGUN system and subtracted the weight of the remaining cement within the MIXIGUN system after each cementation procedure. The recording of the timeframe started with the cement insertion into the femoral canal. During closure, one Redon-drain was left beneath the iliotibial band.

Table 2. Time frame of the drain fluid and serum/blood analysis.

Time	Drain fluid gentamicin	Drain fluid haemoglobin	Serum creatinine	Serum gentamicin	Blood haemoglobin
Pre-op.	–	–	X	–	X
1–2 hours post-op.	–	–	–	X	–
4–8 hours post-op.	X	X	–	X	–
20–28 hours post-op.	X	X	X	X	X
44–52 hours post-op.	X	X	–	X	–
68–76 hours post-op.	X	X	X	X	–
5 days post-op.	–	–	X	–	X

Table 3. Demographics of the study population.

	Thin cement mantle	Thick cement mantle	*p* value
n	16 (12 female)	14 (8 female)	–
Age (years)	72.0 (5.05)	70.9 (4.49)	0.517
BMI (kg/m^2)	25.8 (4.30)	27.9 (18.6)	0.184
Femoral stem	Vectra III (Biomet)	CPT (Zimmer)	–
Acetabular cup	Trilogy (Zimmer)	Trilogy (Zimmer)	–
Cement	HFGBC (AAP)	HFGBC (AAP)	–

Drain fluid, serum and blood analysis

Preoperative serum creatinine and haemoglobin levels were determined in all patients. Postoperatively, the wound drain fluid was collected at 4 time points (Table 2) and the total amount of fluid was measured. Appropriate aliquots of the drainage fluid were collected and transferred to closed sterile vials to assess gentamicin and haemoglobin concentration. The samples were collected and stored according to the Standard Laboratory Method until further quantification gentamicin assays could be performed. The postoperative serum creatinine and blood haemoglobin were determined at 3 time points and the postoperative serum gentamicin at 5 (Table 2).

Statistical analysis

Statistical analysis was performed with SPSS, version 20 (IBM, Chicago, USA). Descriptive statistics were reported as mean (standard deviation). Both treatment groups were compared using the Student's *t*-test. Correlation analyses between drain fluid gentamicin concentration on the one hand and drain fluid volume, drain fluid haemoglobin concentration, and thick or thin cement mantle was performed using the Pearson test for correlation. An analysis of variance (ANOVA) mixed-effects model was applied with drain fluid gentamicin concentration as a dependent variable and drain fluid volume, drain fluid haemoglobin concentration, age, body mass index (BMI), preoperative eGFR, and study group as predictors. Statistical significance was set at $p < 0.05$.

Ethical approval

This study was approved by the ethics committee of the Universitair Ziekenhuis Brussel (approval number 143201316343).

Results

In total 32 patients were approach for the study, 1 person declined leaving 31 participants. Among 31, 16 were randomly allocated to the thin cement mantle group and 15 to the thick cement mantle group. Because of refusal for further blood sampling, one person from the thick cement mantle group was withdrawn from the study leaving 14 participants in that group. Demographics of the remaining 30 participants are shown in Table 3.

One person from the thick cement mantle group experienced a deep wound infection. This person received a THA for a subcapital femur fracture. She was admitted to hospital 13 days after surgery with a purulent deep wound infection with Staphylococcus aureus. She was taking to theatre the same day and a debridement with retention of the prosthesis was performed. She was treated with flucloxacillin and rifampicin for 11 weeks in total. She was followed up in the outpatient clinic regularly and 1 year after the infection she had a pain-free THA and a normal activity of daily living.

The mean amount of cement applied in the thin cement mantle group was significantly smaller than in the thick cement mantle group (Table 4). However, at any stage, the local gentamycin concentration in the drain fluid was not significantly different between groups. In all cases, the local gentamycin concentration was well above the MIC value of 8 mg/L during the first 4–8 hours after the operation (minimum 19.7 mg/L). After 1 day (20–28 hours), 4/16 local gentamicin concentrations in the thin and 1/14 in the thick cement mantle group were inferior to the MIC. After 2 days (44–52 hours), the number of patients with an effective local gentamycin concentration was 1/16 and 2/13 in the thin and thick cement mantel group respectively. After 3 days (68–76 hours), none of the patients was fully protected (maximum 6.5 mg/L) (Figure 1).

Table 4. Amount of cement and gentamicin concentrations in the drain fluid and serum.

	Thin cement mantle $n = 16$	Thick cement mantle $n = 14$	p value
Amount of Cement (mean [SD] in g)	32.5 (6.14)	38.1 (8.00)	0.042
Drain fluid gentamicin (mean [SD] in mg/L)			
Time frame 4–8 hours	57.2 (34.4)	54.9 (19.9)	0.823
Time frame 20–28 hours	18.4 (13.1)	17.1 (11.1)	0.783
Time frame 44–52 hours	2.75 (2.92)	3.69 (3.83)	0.472
Time frame 68–76 hours	1.44 (1.23)	2.17 (1.94)	0.285
Serum gentamicin (mean [SD] in mg/L)			
Time frame 1– 2 hours	0.71 (0.17)[1]	0.70 (0.04)[3]	0.847
Time frame 4–8 hours	0.65 (0.26)[2]	0.77 (0.17)[4]	0.312
Time frame 20–28 hours	nd	nd	
Time frame 44–52 hours	nd	nd	
Time frame 68–76 hours	nd	nd	

SD: standard deviation; nd: no detectable serum concentration levels <0.60mg/L.
[1]$n = 7$ no detectable serum concentration in 8 patients not measured in 1.
[2]$n = 8$ no detectable serum concentration in 7 patients not measured in 1.
[3]$n = 6$ no detectable serum concentration in 7 patients not measured in 1.
[4]$n = 6$ no detectable serum concentration in 8 patients.

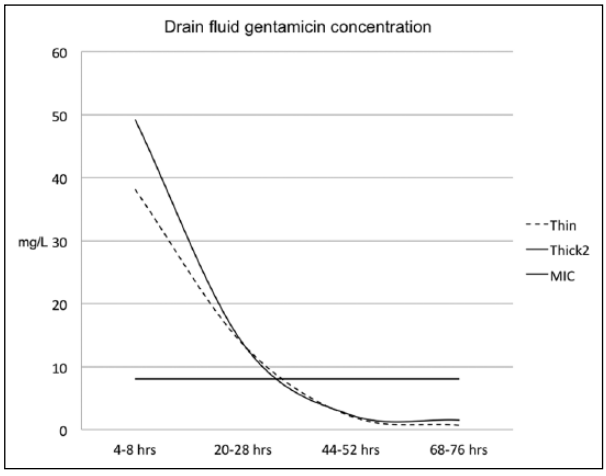

Figure 1. Gentamicin concentration in the drain fluid in the thin and thick cement mantle group at different time intervals.

At any time point, the serum gentamicin concentrations did not differ significantly between the thin and thick cement mantle group. Moreover, the serum gentamicin concentration did not reached the toxic levels of more than 2 mg/L at any time point for any patient. The highest gentamicin concentration (1.08 mg/L) was measured in the thin cement mantle group, 1–2 hours after cement injection. Gentamicin in the serum was undetectable at all times (serum concentration <0.6 mg/L) in 5/16 patients in the thin cement mantle group and in 7/14 in the thick cement mantle group. After 20–28 hours the serum concentration was below the detection limit in all patients.

The preoperative estimated glomerular filtration rate (eGFR) was below 60 ml/minute in 7 out of 30 patients, and none had a preoperative eGFR below 37.8 ml/minute. After the intervention, 6 of these patients presented with an eGFR between 45 and 60 ml/minute. The 7th patient had an eGFR between 75 and 87 ml/minute. Of those 7 patients with mild renal impairment, 5 had a thick cement mantle but none had serum gentamicin levels above 0.73 mg/ml. None of the patients with normal renal function (eGFR >60 ml/minute) developed an acute renal failure at any time point, i.e. an eGFR <60 ml/minute.

4 to 8 hours after surgery, a weak but significant negative correlation was found between drain fluid volume and drain fluid gentamicin concentration, suggesting a dilution effect. After 20–28 hours, a weak but significant positive correlation was found between drain fluid haemoglobin concentration and drain fluid gentamicin concentration (Table 5).

We performed a multiple regression analysis with drain gentamicin concentration at 3 time points as dependent variables and drain fluid volume, drain fluid haemoglobin concentration, age, BMI, preoperative eGFR and study group as predictors. After 4–8 hours and 44–52 hours, the model showed that none of these factors was a significant predictor of the local gentamicin concentration. After 1 day (20–28 hours), the ANOVA model was significant ($p = 0.021$) and could identify pre-op eGFR as a significant negative predictor ($B = -3.15$, $p = 0.006$) and drain fluid haemoglobin ($B = 0.140$, $p = 0.005$) as a significant positive predictor for local gentamicin concentrations.

Discussion

This RCT demonstrated that a femoral hip implant surrounded by a thin or a thick layer of Hi-Fatigue Gentamicin Bone Cement produced similar, effective local gentamicin concentration and similar, safe systemic gentamicin concentration. The impact of the amount of cement surrounding the

Table 5. Pearson's correlation test.

	Drain gentamicin concentration at 4–8 hours	*p* value	Drain gentamicin concentration at 20–48 hours	*p* value	Drain gentamicin concentration at 44–52 hours	*p* value
Study group	−0.043	0.413	−0.052	0.393	0.143	0.229
Drain Hb	0.272	0.077	0.461	0.005	−0.112	0.281
Drain volume	−0.325	0.043	−0.198	0.147	−0.048	0.403

Hb: haemoglobin.

stem on local and systemic gentamicin levels was limited. This confirms the fact that gentamicin release is a diffusion phenomenon that does not depend so much on the total amount of cement used, but rather on the area to volume ratio, as well as the porosity, the surface roughness and wettability of the bone cement.[23,19,20] Moreover, it was recently postulated that the 1st initial high burst is a surface phenomenon and the sustained but much lower release is based on the porosity and the ability of the cement to absorb water.[20]

The composition of bone cement differs between brands and this influences antibiotic release.[23] The powder component of the low viscosity HFGBC used in this study contains polymethyl methacrylate polymer and a high proportion of methyl methacrylate-styrene copolymer (Table 1). Adding styrene copolymers is thought to improve the fatigue strength of the cement, but it remains unclear if this offers clinical significant advantages.[24,25] On the other hand, styrene containing bone cements are more hydrophobic. This decreases the rate of water absorption and will, as such, slow down gentamicin release.[23] Nevertheless, we found that the gentamicin release profile was in line with earlier *in vitro* and *in vivo* studies on primary THA as well as cement spacers and gentamicin loaded beads.[17,26–32]

The gentamicin release profile of HFGBC, showed a high initial burst just after surgery. This resulted in a local gentamicin concentration well above the MIC of 8 mg/L and was followed by a rapid decline within the 1st day. Between the 1st and 2nd postoperative day, the local gentamicin concentration dropped to subtherapeutic levels. As such, gentamicin loaded bone cement might not protect against acute haematogenous infections occurring after a couple of days. However, it might be effective against airborne infections occurring during surgery. After 3 days, the local gentamicin concentration in our study was still detectable (>0.6 mg/L) in 14/25 patients. As drain fluid collection was stopped after that period, we do not know how local gentamicin concentration evolved. It has been shown that low doses of antibiotics can be found in joint aspirates as long as 20 years after implantation.[33] This prolonged release is worrying because subtherapeutic gentamicin concentrations do not protect against haematogenous infections, and may cause antibiotic resistance in subjected strains.[18]

In this study the serum concentration of gentamicin never exceeded the toxic level for prolonged exposure, i.e. 2 mg/L.[12,13] Systemic toxicity of locally delivered antibiotics from bone cement is rare and has only been reported in the presence of high antibiotic concentrations within bone cement used to treat infected implants.[34–36]

Analysing local gentamicin concentrations in regard to possible predictors, we found weak but significant correlations and regression values at a limited number of time points. This might be due to the small sample size, but some relationships cannot really be explained. For example, the relationship between higher haemoglobin concentrations in the drain fluid; suggestive for local bleeding, and higher local gentamicin concentrations is counter-intuitive. On the other hand, higher preoperative eGFR; suggestive for a better renal function, was a predictor for lower local gentamicin concentrations one day after the intervention. This could be explained by the fact that gentamicin clearance depends mostly on renal function. However, all investigated factors were weak predictors of local gentamicin levels and none had a major impact on the high protective concentrations found within 4–8 hours after surgery.

Weaknesses of this study include the fact that we did not investigate the risk of gentamicin toxicity in patients with severe renal impairment, i.e. an eGFR <30 ml/minute. However, 7 patients presented with mild renal failure preoperatively (eGFR between 37 and 60 ml/minute) and none of them developed severe renal failure or presented high serum gentamicin levels. Second, the relative small number of patient might lack power to demonstrate an impact of cement mantle thickness or other patients' factors on local and systemic gentamicin concentrations. On the other hand, overall local gentamicin concentrations were well above the MIC during the 1st 4–8 hours. As such, it would be unlikely that low-impact confounding factors could render gentamicin release ineffective. Similarly, serum gentamicin concentrations remained low and well below the toxic levels for prolonged exposure in all cases, even within the 1st 4–8 hours. Moreover, all serum concentrations became undetectable within the first postoperative day. For this, it seems unlikely that gentamicin release from HFGBC could result in toxic gentamicin serum levels in patients without renal failure.

Conclusion

This RCT investigated the *in vivo* elution kinetics of Hi-Fatigue Gentamicin Bone Cement. The biphasic elution characteristics are in line with earlier studies using other brands of bone cement. As expected the total load of bone cement applied varies in the thick and thin cement mantle group, however since antibiotic elution from bone cement is a surface phenomenon rather than a mass phenomenon, there is no difference in the elution characteristics when applied in a thick or thin cement mantle layer. Local gentamicin concentrations were well above the MIC during the 1st 24 hours in both groups, and none of the patients reached systemic toxic gentamicin levels. Within a day after surgery, all serum gentamicin concentrations decreased below the detection level. After 3 days, detectable gentamicin concentrations in drain fluid were found in only 14 out of 25 patients. This confirms the effectiveness and safety of gentamicin release from High-Fatigue Gentamicin Bone Cement.

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